Journal of Forensic and Legal Medicine 19 (2012) 422–425

Contents lists available at SciVerse ScienceDirect

Journal of Forensic and Legal Medicine

journal homepage: www.elsevier.com/locate/jflm

Case report

A fatal intoxication case involving ropinirole

Sébastien Duband, MD, Doctor [a,*], Carolyne Bidat, MD, Doctor [a], Yvan Gaillard, PharmD, Doctor [b], Max Rochet, MD, Doctor [a], Jean-Philippe Camdessanche, MD, Doctor [c], Michel Péoc'h, MD, PhD, Doctor [d]

[a] Department of Forensic Pathology, University Hospital of Saint-Etienne, Bellevue Hospital, 42055 Saint-Etienne Cedex 2, France
[b] LAT LUMTOX, Laboratory of Analytical Toxicology, 800 Avenue Marie Curie, 07800 La Voulte sur Rhône, France
[c] Department of Neurology, University Hospital of Saint-Etienne, North Hospital, 42055 Saint-Etienne Cedex 2, France
[d] Department of Pathology, University Hospital of Saint-Etienne, North Hospital, 42055 Saint-Etienne Cedex 2, France

ARTICLE INFO

Article history:
Received 9 May 2011
Received in revised form
17 February 2012
Accepted 21 April 2012
Available online 11 May 2012

Keywords:
Ropinirole
Fatal intoxication
Poisoning
Parkinson's disease
Restless legs syndrome

ABSTRACT

Ropinirole, a specific non-ergoline dopamine D2-receptor agonist, belongs to the drugs applied in treatment of Parkinson's disease (PD) and restless legs syndrome (RLS) and acts as a D2, D3, and D4 dopamine receptor agonist with highest affinity for D3. Therapeutic ropinirole plasma levels in adults are defined between 0.4 and 6 ng/mL. This case report documents a fatal intoxication involving ropinirole. Information about lethal ropinirole concentrations is hitherto lacking in the literature and the assessed ropinirole levels of this case may present a step towards defining potentially lethal concentrations. A 37-year-old man without medical history was found dead in a converted van used as place of residence and an autopsy was performed. The pathological findings did not reveal an apparent cause of death but the toxicological analysis revealed the presence of ropinirole, paracetamol, and alcohol in the peripheral blood sample. Quantitative analysis revealed that ropinirole was present at a peripheral blood concentration of 64 ng/mL. The ropinirole concentrations determined in vitreous humor, urine and bile were respectively, 11 ng/mL, 2670 ng/mL and 826 ng/mL. Paracetamol was detected at a blood level of <2 μg/mL. Based on the autopsy findings and toxicological results, the cause of death was primarily attributed to intoxication with ropinirole in combination with alcohol.

© 2012 Elsevier Ltd and Faculty of Forensic and Legal Medicine. All rights reserved.

1. Introduction

Ropinirole ($C_{16}H_{24}N_2O$, 4-[2-(dipropylamino)éthyl]-1,3-dihydro -2H-indol-2-one, Fig. 1), a specific non-ergoline dopamine D2-receptor agonist, belongs to the drugs applied in treatment of Parkinson's disease (PD) and restless legs syndrome (RLS).[1,2] Ropinirole acts as a D2, D3, and D4 dopamine receptor agonist with highest affinity for D3. It appears to be weakly active at the 5-HT2, and α2 receptors and seems to have virtually no affinity for the 5-HT1, benzodiazepine, GABA, muscarinic, α1, and β-adrenoreceptors.[3] Clinical studies have demonstrated its efficacy in the treatment of motor dysfunction in PD as monotherapy[1] or in combination with levodopa.[4] In idiopathic RLS, ropinirole provides a well-tolerated and effective treatment of sensorimotor symptoms. A typical maintenance dose for adult parkinsonian patients, gradually reached over several weeks, ranges from 3 to 9 mg a day, but can be increased to 24 mg. For RLS, the effective daily doses are lower and range from 2 to 4 mg. Peak plasma levels are usually attained 1.5 h after oral administration of a single dose of immediate release form but absorption may be delayed by an average of 2 h after consuming a meal high in fat compared with the fasting state.[5] Its bioavailability is about 50% (36–57%) with highly variable plasma protein binding (10–40%), an overall volume of distribution of about 7.5 L/kg and a half-life in plasma of 6 h. After 2 days of use, steady state concentrations are generally achieved. Therapeutic ropinirole plasma levels in adults are defined between 0.4 and 6 ng/mL.[6] Since the pharmacokinetics of ropinirole have not been studied in patients with hepatic impairment it should be titrated with caution in patients with hepatic insufficiency. No specific modifications in dosing are necessary in patients with mild to moderate renal insufficiency as characterized by a creatine clearance of 30–50 mL/min because only 10% of the drug is excreted unchanged in urine. Ropinirole has not been studied in patients with severe renal impairment.

Ropinirole is metabolized primarily by cytochrome P450 CYP1A2, and at doses higher than clinical, is also metabolized by CYP3A4. At doses greater than 24 mg, CYP2D6 may be inhibited, although this has only been tested *in vitro*. The major metabolite displays a pharmacologic activity 100 times lesser effective than ropinirole.

* Corresponding author. Tel.: +33 (0) 4 77 12 05 23; fax: +33 (0) 04 77 12 09 16.
E-mail address: sebastien.duband@chu-st-etienne.fr (S. Duband).

1752-928X/$ – see front matter © 2012 Elsevier Ltd and Faculty of Forensic and Legal Medicine. All rights reserved.
doi:10.1016/j.jflm.2012.04.013

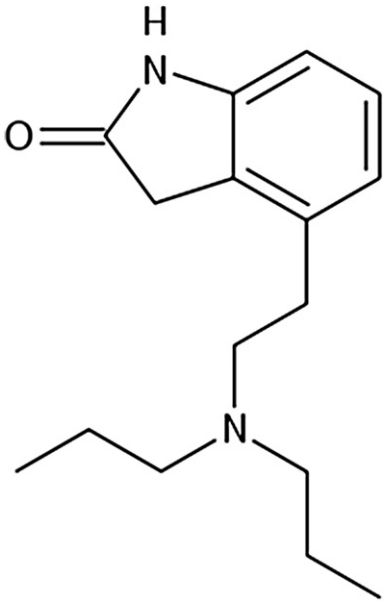

Fig. 1. Chemical structure of ropinirole.

In the early PD study, adverse effects were similar between ropinirole prolonged and immediate release formulations. The adverse events that occurred in greater than 5% of subjects in either treatment group included nausea (19% prolonged release, 20% immediate release), somnolence (11% prolonged release, 15% immediate release), dizziness (6% prolonged and immediate release), headache (6% prolonged release, 5% immediate release), constipation (5% prolonged and immediate release), dyspepsia (3% prolonged release, 7% immediate release) and fatigue (3% prolonged release, 5% immediate release).[7] In the advanced PD study, the most common adverse effects noted with ropinirole prolonged release vs placebo included the development of dyskinesia (13% vs 3%), nausea (11% vs 4%), dizziness (8% vs 3%), somnolence (7% vs 4%), hallucinations (6% vs 1%), and orthostatic hypotension (5% vs 2%).[8] There is only few data about ropinirole toxicity but, recently, repetitive torsades de pointes (type of ventricular tachycardia) or other types of cardiac arrhythmias have been observed in ropinirole-treated patients.[9,10] Furthermore, some experimental *in vitro* and animal studies have suggested that this treatment may carry proarrhythmic risk for patients especially in cases of accidental overdose or intoxication by demonstrating an inhibition of the rapid delayed rectifier K^+ current under supratherapeutic concentrations.[11,12] Although ropinirole is a widely used drug, there is no report of fatal human poisoning to our knowledge.

In this article, we present a case of a fatal ropinirole poisoning. Information about lethal ropinirole concentrations is hitherto lacking in the literature and the assessed ropinirole levels of this case may present a step towards defining potentially lethal concentrations.

2. Case history

A 37-year-old man without medical history was found dead by his brother leaving him alone for approximately 24 h in a converted van used as place of residence. The body was on the right side, lying on the couchette, with the hanging legs. Initial police inquiry was inconclusive. There was no indication of burglary, any suicide note or evidence for a fight. No drugs tablet or blister was found near the body. Police records revealed that 24 h earlier both brothers had gone in a party in the course of which they had consumed some alcohol. Because of the mechanism of death remained unknown after the first observations, a forensic autopsy was ordered and performed to eliminate a possible criminal action.

3. Material and methods

A standard autopsy was performed according to current guidelines 36 h after the body's discovery and samples of each major organ and injured tissue were histologically analyzed after formalin fixation, embedding in paraffin and hematoxylin–eosin–saffron staining. Furthermore, a comprehensive systematic toxicological screening (STA) procedures including head-space gas chromatography–mass spectrometry (GC–MS) for the analysis of ethanol and other volatile substances, GC–MS after acetylation with the use of CARIBOU® software,[13] high performance liquid chromatography photodiode array detection (HPLC-PDA),[14] UPLC-PDA/MS,[15] UPLC-MS/MS screenings[16,17] as well as immunoassay techniques, carbon monoxide and cyanide detection was conducted.

4. Results

4.1. Autopsy findings

External examination exhibited a normally developed Caucasian man of normal corpulence (173 cm, 62 kg) showing no remarkable external injuries. The inspection revealed fixed post-mortem lividity of normal intensity and location corresponding to the position of the body when it was discovered and early putrefactive change with green discoloration of the lower abdomen. Examination of internal organs demonstrated pulmonary oedema (lungs weight = 1134 g, Normal: 825–950 g) without aspiration phenomenon. The gastric content (300 mL) didn't show drug particles. No cardiac hypertrophy or additional pulmonary pathology was observed. The coronary arteries showed no remarkable signs of atherosclerosis. Furthermore, no tongue bite or other indications for an epileptic seizure were found. Systematic microscopic examination confirmed intra-alveolar pulmonary oedema and generalized vascular congestion predominantly in liver. Overall, the pathological findings did not reveal an apparent cause of death.

For toxicological analyses, the following samples were collected: vitreous humor, femoral blood, bile, gastric contents and urine.

4.2. Toxicological results

The results revealed the presence of ropinirole, paracetamol, and alcohol in the peripheral blood sample. No illegal drugs were detected. The blood alcohol level was 2.26 g/L, the alcohol concentration in urine was 2.94 g/L. Quantitative analysis revealed that ropinirole was present at a peripheral blood concentration of 64 ng/mL. The ropinirole concentrations determined in vitreous humor, urine and bile were respectively 11 ng/mL, 2670 ng/mL and 826 ng/mL. Paracetamol was detected at a blood level of <2 μg/mL. The concentrations measured in urine and bile were similar to those in peripheral blood sample (see Table 1).

Table 1
Summary of the toxicological results in the different matrices used.

	Peripheral blood	Urine	Bile	Vitreous humor
Ropinirole	64 ng/mL	2670 ng/mL	826 ng/mL	11 ng/mL
Paracetamol	<2 μg/mL	<2 μg/mL	<2 μg/mL	<2 μg/mL
Alcohol	2.26 g/L	2.94 g/L	NA	NA

5. Discussion

There is little information in the literature regarding toxic or fatal blood concentrations of ropinirole. No case of serious or lethal ropinirole intoxication has already been described. Especially post-mortem data concerning ropinirole concentrations in biological matrices are not available. To our knowledge, we report the first case of fatal ropinirole intoxication for which concentrations have been determined in peripheral blood as well as in urine and bile. The detected peripheral blood concentration of 64 ng/mL clearly exceeds the therapeutic range indicated in the literature (0.4–6 ng/mL) and is likely to induce severe cardiac arrhythmia.[6,9–11] Cardiac side effects have already been described for usual concentrations during the titration phase of therapeutic adjustment. These effects correspond to syncopes, atrial fibrillations[10] and torsades de pointe.[9] Syncope was observed in several clinical trials of ropinirole in Parkinson's disease although with low incidence when the drug was gradually increased.[18]

The mechanisms of cardiac toxicity of this molecule, although incompletely clarified, begin to be understood. Ropinirole is a dopamine agonist with high selectivity for both peripheral and central D2 dopamine receptors (subtypes D2, D3, and D4). It has a higher affinity for D3 dopamine receptors. The final effect of ropinirole is an increased vagal activity, probably linked to different mechanisms:

1. The stimulation of D2 presynaptic receptors, reduces the epinephrine release in the synapse[19];
2. The stimulation of D2/D3 striatal receptors increases the parasympathetic activity.[20]

Both cardiac adverse events seemingly triggered by ropinirole, i.e., severe bradycardia and atrial fibrillation, can be induced by a resulting excess of vagal activity. Intense vagal stimulations can lead to phenomenon of macroreentry in atrial cells, promoting atrial arrhythmias.[21] Furthermore, some animal or *in vitro* experimental studies have shown a suppressive effect of ropinirole high doses on HERG (human ether-à-go-go-related gene) channels current. A study on Chinese hamster ovary cells expressing HERG channel gene demonstrated a suppressive effect on HERG current for ropinirole concentrations range from 31.42 to 3142 ng/mL explaining a prolongation of the cardiac action potential and/or an increase of the QT interval[11] (a well-known risk factor for the development of the potentially life threatening ventricular arrhythmia *torsades de pointes*[22]). On canine ventricular myocytes, Simkò et al. show that, for high concentrations ($\geq$314.2 ng/mL), ropinirole increased action potential duration and suppressed the rapid delayed rectifier K^+ current carrying proarrhythmic condition.[9] Finally, Humphrey et al. conclude that ropinirole, for peak plasma level of 3.5 ng/mL, significantly prolongs QTc by over 33 ms in conscious dogs and can trigger serious ventricular arrhythmia such as *torsade de pointes*.[12]

The toxicological results confirmed the preliminary morphological findings that were concordant with an acute intoxication. The autopsy revealed usual signs found in cardiac arrhythmia cases such as intra-alveolar pulmonary oedema and diffuse visceral congestion. No indications for an epileptic seizure or pre-existing cardiovascular or pulmonary pathology have been found.

Recently, Navacerrada et al. have reported a case of cholestatic injury associated with hepatic cytolysis related with ropinirole use for restless legs syndrome and developed 3 months after the beginning of the treatment.[23] This liver toxicity is in relation with a chronic absorption. In our case, no jaundice was noticed and microscopic examination of hepatic tissue didn't show any sign of drug-induced hepatitis. This result tends to demonstrate that the acute ropinirole toxicity is not hepatic.

The role of concomitant alcohol intoxication can be discussed but there was no argument for an associated metabolic disorder (no ketoacidosis) or hypothermia. Moreover, there was no sign at autopsy of pre-existing consciousness loss or coma before death (no vomit aspiration) suggesting a sudden cardiac death. Alcohol intoxication seems to have played a minor role in the fatal issue here.

In our case, the remaining question is the nature of this overdose. In fact, this man wasn't known to be affected by Parkinson's disease or restless legs syndrome. No suicide note has been left and his medical history didn't involve depressive disorders or suicidal attempts. A deliberate misuse has been suggested compared with the well-known misuse of other antiparkinsonian drugs such as trihexyphenidyl for its hallucinogenic and euphoric effects.[24] Ropinirole can cause hallucinations and rarer and more unusual side effects specific to D_3-preferring agonists such as hypersexuality and compulsive gambling, even in patients without a prior history of these behaviors.[25] However, the toxicological results don't substantiate this hypothesis because no narcotic or other drugs (often associated with trihexyphenidyl) were found in analyzed matrices. An accidental or criminal overdose cannot be ruled out completely but it was not possible to investigate further details concerning this overdose.

In conclusion, the present case demonstrates a fatal intoxication involving the antiparkinsonian drug ropinirole. The assessed ropinirole concentration of 64 ng/mL in peripheral blood clearly exceeds the therapeutic range and may represent a highly cardiac toxic, even lethal concentration. The presented post-mortem data may help to define potentially lethal ropinirole concentrations.

Conflict of interest

None.

Funding

None.

Ethical approval

None.

References

1. Vidaihlet M, Bonnet AM, Belal S, Dubois B, Marle C, Agid Y. Ropinirole without levodopa in Parkinson's disease. *Lancet* 1990;**336**:316–7.
2. Trenkwalder C, Hening WA, Montagna P, Oertel WH, Allen RP, Walters AS, et al. Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. *Mov Disord* 2008;**15**:2267–302.
3. Eden RJ, Costall B, Domeney AM, Gerrard PA, Harvey CA, Kelly ME, et al. Preclinical pharmacology of ropinirole (SK&F 101468-A) a novel dopamine D2 agonist. *Pharmacol Biochem Behav* 1991;**38**:147–54.
4. Rascol O, Lees AJ, Senard JM, Pirtosek Z, Montastruc JL, Fuell D. Ropinirole in the treatment of levodopa-induced motor fluctuations in patients with Parkinson's disease. *Clin Neuropharmacol* 1996;**19**:234–45.
5. *Requip (ropinirole hydrochloride): US prescribing information*. Glaxo-SmithKline; 2006.
6. Tompson DJ, Vearer D. Steady-state pharmacokinetic properties of a 24-Hour prolonged-release formulation of ropinirole: results of two randomized studies in patients with Parkinson's disease. *Clin Ther* 2007;**29**:2654–66.
7. Stocchi F, Hersh BP, Scott BL, Nausieda PA, Giorgi L. Ropinirole 24-hour prolonged release and ropinirole immediate release in early Parkinson's disease: a randomized, double-blind, non-inferiority crossover study. *Curr Med Res Opin* 2008;**24**:2883–95.
8. Pahwa R, Stacy MA, Factor SA. Ropinirole 24-hour prolonged release: randomized, controlled study in advanced Parkinson disease. *Neurology* 2007;**68**:1108–15.
9. Simkó J, Szentandrássy N, Harmati G, Bárándi L, Horváth B, Magyar J, et al. Effects of ropinirole on action potential characteristics and the underlying ion currents in canine ventricular myocytes. *Naunyn Schmiedebergs Arch Pharmacol* 2010;**382**:213–20.
10. Di Giacopo R, Fasano A, Fenici R, Loria G. Rare and serious cardiac side effects during ropinirol titration. *Mov Disord* 2010;**25**:1509–10.
11. Hurst RS, Higdon NR, Lawson JA, Clark MA, Rutherford-Root KL, McDonald WG, et al. Dopamine receptor agonists differ in their actions on cardiac ion channels. *Eur J Pharmacol* 2003;**482**:31–7.

12. Humphrey SJ, Turman CN, Curry JT, Wheeler GJ. Cardiovascular and electrocardiographic effects of the dopamine receptor agonists ropinirole, apomorphine, and PNU-142774E in conscious beagle dogs. *J Cardiovasc Pharmacol* 2006;**47**:337–47.
13. Bévalot F, Gaillard Y, Lemeur C. Utilisation de macro-commandes pour l'optimisation de l'exploitation des chrommatogrammes de dépistages systématiques obtenus en GC/MS, *11th Congress of the Société Française de Toxicologie Analytique*. Dinard, June 10–13, 2003.
14. Gaillard Y, Pépin G. Use of high performance liquid chromatography with photodiode-array UV detection for the creation of a 600-compound library. Application to forensic toxicology. *J Chromatogr A* 1997;**763**:149–63.
15. Chatenay C, Bévalot F, Gaillard Y. Use of UPLC-PDA/MS in systematic toxicological analysis. *47th Congress of the international association of forensic toxicologists*. Genova, August 23–29, 2009.
16. Sauvage FL, Gaulier JM, Lachâtre G, Marquet P. Pitsfall and prevention strategies for liquid chromatography tandem mass spectrometry in the selected reaction-monitoring mode for drug analysis. *Clin Chem* 2008;**54**:1519–27.
17. Sauvage FL, Saint-Marcoux F, Duretz B, Delporte D, Lachâtre G, Marquet P. Screening of drugs and toxic compounds with liquid chromatography-linear ion trap tandem mass spectrometry. *Clin Chem* 2006;**52**:1735–42.
18. Szymanski C, Boey S, Hermida JS. Ropinirole-induced symptomatic sinus node dysfunction. *Pacing Clin Electrophysiol* 2008;**31**:1079–82.
19. Mannelli M, Lazzeri C, Ianni L, La Villa C, Pupilli C, Bellini F, et al. Dopamine and sympathoadrenal activity in man. *Clin Exp Hypertens* 1997;**19**:163–79.
20. Yeh TL, Yang YK, Chiu NT, Yao WJ, Yeh SJ, Wu JS, et al. Correlation between striatal dopamine D2/D3 receptor binding and cardiovascular activity in healthy subjects. *Am J Hypertens* 2006;**19**:964–9.
21. Coumel P. Paroxysmal atrial fibrillation: role of autonomic nervous system. *Arch Mal Coeur Vaiss* 1994;**87**:55–62.
22. Redfern WS, Carlsson L, Davis AS, Lynch WG, MacKenzie I, Palethorpe S, et al. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. *Cardiovasc Res* 2003;**58**:32–45.
23. Navacerrada F, González-Alonso MR, Alonso-Navarro H, Pilo-de-la-Fuente B, Plaza-Nieto JF, Jiménez-Jiménez FJ. Liver toxicity possibly related with ropinirole use in the treatment of restless legs syndrome. *Eur J Neurol* 2011;**18**(6):e65. doi:10.1111/j.1468-1331.2010.03317.x.
24. Frauger E, Thirion X, Chanut C, Natali F, Debruyne D, Saillard C, et al. Misuse of trihexyphenidyl (Artane, Parkinane): recent trends. *Therapie* 2003;**58**:541–7.
25. Cornelius JR, Tippmann-Peikert M, Slocumb NL, Frerichs CF, Silber MH. Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. *Sleep* 2010;**33**:81–7.